A B C D

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DRUG INFORMATION

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Dear Mr. Citron:

Thank you for discussing MICARDIS® Tablets (telmisartan) with your Boehringer Ingelheim Pharmaceuticals, Regional Manager, State Government Affairs, Penny Atwood. You requested information regarding the following topic(s):

- ONTARGET Trial
- Renoprotective Effects
- TRENDY Trial

If you did not request this information, please contact our Drug Information Unit Call Center at 1-800-542-6257 (option #4).

MICARDIS Tablets is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. Any other use not included in the package insert(s) is an investigational use and cannot be recommended by Boehringer Ingelheim Pharmaceuticals, Inc.

Thank you for your interest in MICARDIS Tablets. If you should have any further questions, please do not hesitate to contact the Drug Information Unit.

Sincerely,

Eric J. Polistena, Pharm.D.

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ONTARGET Trial

The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) was an international, multicenter, randomized, double-blind study, in which patients at high risk of cardiovascular events, but with well controlled blood pressure were followed for 3.5 to 5.5 years. The Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) is a parallel study completing later in 2008, that examines the benefit of telmisartan over placebo in ACE intolerant patients with a similar patient population and endpoints. In ONTARGET, high-risk patients with coronary, peripheral vascular, or cerebrovascular disease, or diabetes with end-organ damage were randomized in a ratio 1:1:1 to telmisartan, ramipril, or telmisartan + ramipril. Twenty five thousand, six hundred and twenty patients were randomized into ONTARGET from 733 centers in 40 countries. The primary objectives of ONTARGET were to determine if telmisartan 80 mg daily and ramipril 10 mg daily combination therapy was more effective in reducing the composite endpoint of cardiovascular mortality, acute myocardial infarction, stroke, or hospitalization for congestive heart failure compared with ramipril 10 mg alone; and telmisartan 80 mg daily was at least as effective as ramipril 10 mg daily, on this endpoint.[1, 2, 3]

The secondary objectives were to determine and compare the effects of the treatments to the HOPE (Heart Outcomes Prevention Evaluation) study primary endpoints, as well as the incidence of newly diagnosed congestive heart failure, revascularization procedures, newly diagnosed diabetes, cognitive decline and dementia, nephropathy, and new onset atrial fibrillation.[1,2,5] The secondary endpoint of nephropathy in the study was defined by the presence of any one of the following criteria: 24 hour urinary albumin greater than 300 mg, 24 hour total protein greater than 500 mg, a timed albumin excretion rate greater than or equal to 200 mcg/min, in the absence of a 24 hour urine result a measured urinary albumin/creatinine ratio greater than 36 mg/micromole, doubling of baseline serum creatinine (applicable only to individuals with creatinine levels greater than 1.3 mg/dL), or requiring dialysis.[4] The criteria used for diagnosing new onset diabetes during the study were the following: elevated laboratory values with either elevated fasting plasma glucose ≥ 7mmol/L, or elevated HbA1c ≥ 110% of upper limit of normal for the center, or locally measured 2 hour ≥ 11.1mmol/L following a 75 gram oral glucose tolerance test (OGTT), or initiation of anti-diabetic medication (either an oral hypoglycemic drug or insulin).[4]

In order to compare the results of ONTARGET with those of the HOPE study, the study design, patient population and primary outcomes were carefully chosen to mirror those of HOPE. The primary outcomes for ONTARGET were extended from those of HOPE, and include hospitalization for heart failure in addition to incidence of cardiovascular death, myocardial infarction or stroke.[2, 5]

Inclusion Criteria:
The population in the trial was comprised of patients 55 years of age or older, who were at high risk of developing a major CVD event, and who had a history of coronary artery disease, peripheral arterial occlusive disease, a previous cerebrovascular event, or high-risk diabetes (insulin-dependent or non-insulin-dependent) with evidence of target organ damage. Coronary artery disease was defined as previous myocardial infarction, or stable or unstable angina with documented multivessel CAD, or multivessel PTCA, or multivessel CABG without angina or with recurrent angina after surgery. Cerebrovascular event was defined as previous stroke (included definite or presumed cerebral infarction, intracerebral hemorrhage, stroke of uncertain subtype, but NOT subarachnoid hemorrhage), TIA (transient ischemic attack) > 7 days and < 1 year.[1] TIA was defined as acute loss of focal cerebral or monocular function with symptoms lasting < 24 hours, and which is thought to be due to inadequate cerebral or ocular blood supply as a result of arterial thrombosis or embolism.[4] Peripheral arterial occlusive disease (PAOD) was defined as previous limb bypass surgery or angioplasty, previous limb or foot amputation, intermittent claudication (ankle/arm index ≤ 0.8 on at least one side), significant peripheral arterial stenosis (> 50%) by angiography or non-invasive testing.[1] The criteria for diabetes with end organ damage included: retinopathy, macro or microalbuminuria, or any evidence of previous cardiac or vascular disease. Diabetics were not distinguished into type 1 and 2 within the study.[4] *(See Table 1)*

Exclusion Criteria:
Patients were excluded from study entry if they had any of the following: an inability to discontinue ACE-inhibitors or angiotensin receptor antagonists prior to study entry, a known intolerance to ACE-inhibitors, symptomatic

congestive heart failure, hemodynamically significant primary valvular or outflow tract obstruction, constrictive pericarditis, uncontrolled hypertension on treatment (BP>160/100 mmHg), heart transplant recipient, strokes due to subarachnoid hemorrhage, documented significant renal artery stenosis, creatinine clearance < 36 ml/min or serum creatinine >3.0 mg/dL, serum potassium >5.5 mmol/L, or hepatic dysfunction.[1] *(See Table 1)*

Table 1: Inclusion and Exclusion Criteria used in ONTARGET[1, 4]

Inclusion	
Individuals ≥55 years of age with one of the following:	
Coronary Artery Disease	Previous myocardial infarction (>2 days post uncomplicated MI) Stable angina or unstable angina >30 days before informed consent and documented evidence of multi-vessel coronary artery disease Multi-vessel PTCA >30 days before informed consent Multi-vessel CABG surgery >4 yrs before informed consent, or with recurrent angina following surgery
Peripheral Artery Disease	Previous limb bypass surgery or angioplasty Previous limb or foot amputation Intermittent claudication, with ankle/arm index ≤ 0.8 on at least one side Significant peripheral artery stenosis (>50%) documented by angiography or non-invasive testing
Cerebrovascular Disease	Previous stroke Transient ischemic attacks >7 days and <1 yr before informed consent
Diabetes Mellitus	Diabetics with evidence of end organ damage
Exclusion	
Medication Use	Unable to discontinue ACEI or ARB Known hypersensitivity or intolerance to ACEI or ARB (patients intolerant to ACEI may be enrolled in TRANSCEND)
Cardiovascular disease	Symptomatic congestive heart failure Hemodynamically significant primary valvular or outflow tract obstruction Constrictive pericarditis Complex congenital heart disease Syncopal episodes of unknown etiology <3 months before informed consent Planned cardiac surgery or PTCA <3 months of informed consent Uncontrolled hypertension on treatment (>160/100 mmHg) Heart transplant recipient Stroke due to subarachnoid hemorrhage
Other conditions	Significant renal artery disease Creatinine clearance <36 ml/min or serum creatinine ≥3.0 mg/dL Serum potassium > 5.5 mmol/L Hepatic dysfunction Uncorrected volume or sodium depletion Primary hyperaldosteronism Hereditary fructose intolerance Other major noncardiac illness expected to reduce life expectancy or interfere with participation in study Taking any other experimental drug during the study Significant disability precluding regular follow-up visits Unable or unwilling to provide informed consent

The patients within ONTARGET had similar physical characteristics to those of patients in the HOPE study in regards to age, gender, body mass index, and waist:hip ratio, but ONTARGET had greater ethnic diversity, with approximately 14% of the total patient population recruited from Asian countries. At baseline, the distribution and

type of co-morbidity in ONTARGET and HOPE were comparable, with the majority of patients having a history of coronary artery disease or diabetes mellitus. Two-thirds of the ONTARGET patients had a history of hypertension, versus about half of the patients in HOPE, but the proportion of patients with diabetes was the same in both trials.[2] Also, the patients in ONTARGET were a little older, and a higher proportion had a history of stroke or TIA, as compared to HOPE.[1, 2] Further, more patients in HOPE had angina, but the percentage of patients in both trials with a history of prior cardiovascular event was similar. Altered cardiovascular surgery practices during recent years, was reflected in the surgical histories of patients in each trial. Patients in HOPE were more likely to have undergone coronary artery bypass graft, and more patients in ONTARGET had a history of percutaneous transluminal coronary angioplasty or percutaneous coronary intervention.[2]

The baseline use of medicines known to reduce mortality/morbidity, such as beta-blockers, lipid-lowering therapy, ACE inhibitors, and angiotensin receptor antagonists is higher in ONTARGET. A little over half of the ONTARGET patients received beta-blockers, compared to just over a third of patients in HOPE. Statins were used by 28.9% of patients in HOPE, versus 61.6% at baseline, (increasing to 70.6% by the end of the study) in ONTARGET. The baseline characteristics of the 25,620 patients in ONTARGET were similar among the three study groups: 27% were women, 85% had cardiovascular disease, 69% had hypertension, and 38% had diabetes.[3] Prior to the run-in phase of ONTARGET, the mean blood pressure among the three treatment groups was 141.8/82.1 mmHg. Also, the mean blood pressure at randomization for ONTARGET was 134/77 mmHg, which was similar to the entry BP of 139/79 mmHg in HOPE.[1] All patients were required to stop ACE inhibitor and ARB treatment during the run-in phase, and there was no washout period for patients who had previously been on either drug class.[1, 2] *(See Table 2)*

Table 2: Baseline Patient Demographics Comparison for ONTARGET and HOPE[1, 2, 3]

Baseline Characteristics	**ONTARGET**	**HOPE**
Age, years	66.4	65.9
Male, %	73.3	73.3
BMI, kg/m^2	28.2	27.7
Waist-hip ratio	0.9	0.9
Potassium (mmol/L)	4.4	4.4
Medical History (%)		
MI	48.7	52.8
Stable angina	34.8	55.8
Unstable angina	14.8	25.7
Hypertension	68.3	46.5
Diabetes	37.2	38.3
Stroke/TIA	20.7	10.8
Baseline Medications (%)		
ACE inhibitors	57.5	11.6
ARBs	8.6	0
Beta-blockers	56.9	39.5
Diuretics	27.9	15.1
Nitrates	29.2	31.1
Diltiazem/verapamil	9.7	27.1
Other CCBs	23.8	20.5
Aspirin	75.6	73.6
Oral anticoagulants	7.6	3.8
Statins	61.6	28.9
Fibrates	4.5	0
Insulin	10.4	11.7
Oral hypoglycemics	25.0	21.8

Run-in and Randomization Schedule:

Patients were forced titrated to telmisartan 80 mg and ramipril 10 mg. Patients underwent a single-blind run-in phase in which they received ramipril 2.5 mg once daily for 3 days, followed by telmisartan 40 mg plus ramipril 2.5 mg once daily for 7 days, and then ramipril 5 mg plus telmisartan 40 mg for 11 to 18 days.[3] Those patients who remained eligible after the run-in phase, were randomized during the first two weeks to telmisartan 80 mg (n=8542), or ramipril 5 mg (n=8576), or ramipril 5 mg plus telmisartan 80 mg (n=8502). After 2 weeks, the dose of ramipril was uptitrated to 10 mg, with patients receiving either telmisartan 80 mg, ramipril 10 mg, or ramipril 10 mg plus telmisartan 80 mg daily.[3] Patients continued on these doses for the remainder of the study. The patients could be down titrated, if necessary due to an adverse event as per investigator instructions.[4] The concomitant medications allowed during ONTARGET were beta-blockers, diuretics, nitrates, diltiazem/verapamil, other calcium-channel blockers, aspirin, ticlopidine, clopidogrel, oral anticoagulants, statins, fibrates, insulin, oral hypoglycemics, estrogen (in females) and estrogen plus progesterone (in females).[1] After randomization, follow-up visits were made at 6 weeks, 6 months later, and then every 6 months until the last scheduled visit.[1,3] After the run-in phase, 3399 patients (11.7%) were excluded from the study. The reasons for non-randomization after the run-in phase were very similar to those of HOPE and included: 1123 (3.9%) for poor compliance, 597 (2.1%) withdrew from the study, 492 (1.7%) had symptomatic hypotension, 223 (0.8%) had elevated potassium, 64 (0.2%) had elevated creatinine, 872 (3.0%) had other reasons for exclusion and 27 (0.1%) had died.[2, 3]

Statistical Analysis:

Superiority and non-inferiority for ONTARGET were evaluated using group sequential tests at a 1-sided level α = 0.025, with 3 planned interim analyses. The independent Data Safety and Monitoring Board met twice yearly; the three formal interim analyses were performed, when 25%, 50%, and 75% of the events had been collected. All analyses were intention to treat, and included all randomized patients. The primary endpoint was analyzed on a time to first event occurrence for the composite of cardiovascular mortality, acute myocardial infarction, stroke, or hospitalization for congestive heart failure. Secondary outcomes for ONTARGET were also explored in a similar manner. Primary study outcomes were adjudicated by a central adjudicator, using essential information supporting the diagnoses, such as electrocardiographic and cardiac enzyme results for MI or computed tomography scans for strokes. Additional information was requested as needed, and all agreed upon events were included in the analysis.[1]

Results:

At a median follow-up of 56 months, the primary outcome occurred in 1412 patients (16.5%) in the ramipril group, in 1423 patients (16.7%) in the telmisartan group, and in 1386 patients (16.3%) in the combination therapy group *(See Table 3)*. The upper limit of the confidence interval (1.09) for the relative risk of the primary outcome in the telmisartan group compared to the ramipril group was significantly lower than the noninferiority boundary of 1.13 (p=0.004) defined prior to the study. However, the lower limit of the confidence interval (0.94) shows that telmisartan was not superior to ramipril. The secondary outcome of death from cardiovascular causes, myocardial infarction, or stroke, occurred in 1210 patients (14.1%) in the ramipril group and in 1190 patients (13.9%) in the telmisartan group (relative risk, 0.99; 95% confidence interval [CI], 0.91 to 1.07; p=0.001 for noninferiority), showing no difference between the groups. The results were consistent for all of the primary outcome measures. Also in regards to the primary outcome, the combination therapy was not significantly better than ramipril alone (relative risk, 0.99; 95% CI, 0.92 to 1.07).[3]

At 6 weeks, mean blood pressure was reduced by -6.4/-4.3 mmHg in the ramipril group, by -7.4/-5.0 mmHg in the telmisartan group, and -9.8/-6.3 mmHg in the combination therapy group. Throughout the rest of the study, the mean blood pressure was lower in both the telmisartan (a -0.9/-0.6 mmHg greater reduction) and the combination therapy groups (a -2.4/-1.4 mmHg greater reduction) than in the ramipril group, although the lower levels did not lead to further benefit. Adjustments for the small differences in blood pressure did not essentially alter the results for the primary outcome. [3]

There was no significant difference in the total number of deaths between the ramipril and the telmisartan groups (1014 deaths and 989 deaths, respectively; relative risk in the telmisartan group, 0.98; 95% CI, 0.90 to 1.07). The number of deaths was higher in the combination therapy group than in the ramipril group (1065 deaths vs. 1014 deaths, although this difference was not significant; relative risk in the combination therapy group, 1.07; 95% CI,

0.98 to 1.16). Analyses of the cause of death did not show significant differences with respect to any particular cause.[3]

Except for renal dysfunction, which occurred in 871 (10.2%) patients in the ramipril group, 906 (10.6%) patients in the telmisartan group, and 1148 (13.5%) patients in the combination therapy group, there were no significant differences in the rates of secondary outcomes *(See Table 4)*. While the combination therapy group had a significant increase in the relative risk (1.33, p<0.001) of renal impairment, the telmisartan group had a similar relative risk of renal impairment (1.04; 95% CI, 0.96 to 1.14) compared with the ramipril group. The rate of dialysis was the same in the telmisartan group and the ramipril group, with 52 (0.6%) patients and 48 (0.6%) patients, respectively, undergoing dialysis. The rate was increased in the combination therapy group, with 65 (0.8%) patients undergoing dialysis (p=0.10 for the comparison to the ramipril group).[3]

Table 3: Incidence of the Primary Outcome, Its Components, and Death from Any Cause[3]

	Ramipril (n=8576)	**Telmisartan (n=8542)**	**Combination Therapy (n=8502)**	**Telmisartan versus Ramipril**	**Combination versus Ramipril**
	Number (Percent)			**Risk Ratio (95% CI)**	
Outcome					
Death from CV causes, MI, stroke, or hosp. for heart failure*	1412 (16.5)	1423 (16.7)	1386 (16.3)	1.01 (0.94 to 1.09)	0.99 (0.92 to 1.07)
Death from CV causes, MI, or stroke†	1210 (14.1)	1190 (13.9)	1200 (14.1)	0.99 (0.91 to 1.07)	1.00 (0.93 to 1.09)
Myocardial Infarction‡	413 (4.8)	440 (5.2)	438 (5.2)	1.07 (0.94 to 1.22)	1.08 (0.94 to 1.23)
Stroke‡	405 (4.7)	369 (4.3)	373 (4.4)	0.91 (0.79 to 1.05)	0.93 (0.81 to 1.07)
Hosp. for heart failure‡	354 (4.1)	394 (4.6)	332 (3.9)	1.12 (0.97 to 1.29)	0.95 (0.82 to 1.10)
Death from CV causes	603 (7.0)	598 (7.0)	620 (7.3)	1.00 (0.89 to 1.12)	1.04 (0.93 to 1.17)
Death from non-CV causes	411 (4.8)	391 (4.6)	445 (5.2)	0.96 (0.83 to 1.10)	1.10 (0.96 to 1.26)
Death from any cause	1014 (11.8)	989 (11.6)	1065 (12.5)	0.98 (0.90 to 1.07)	1.07 (0.98 to 1.16)

* Patients could have multiple events in this category. The number of events were 2058 (24.0%) in the ramipril arm, 2042 (23.9%) in the telmisartan arm, and 2000 (23.5%) in the combination therapy arm. The differences were not significant (p=0.83 for telmisartan versus ramipril, and p=0.38 for combination therapy versus ramipril).
† This composite was the primary outcome in the Heart Outcomes Prevention Evaluation (HOPE) trial.
‡ Patients could have multiple events in this category. The category includes both fatal and nonfatal events.

Table 4: Secondary and Other Outcomes[3]

	Ramipril (n=8576)	**Telmisartan (n=8542)**	**Combination Therapy (n=8502)**	**Telmisartan versus Ramipril**	**Combination versus Ramipril**
	Number (Percent)			**Relative Risk (95% CI)**	
Outcome					
Revascularization	1269 (14.8)	1290 (15.1)	1303 (15.3)	1.03 (0.95 to 1.11)	1.04 (0.97 to 1.13)
Hospitalization for angina	925 (10.8)	954 (11.2)	952 (11.2)	1.04 (0.95 to 1.14)	1.04 (0.95 to 1.14)
Worsening or new angina	567 (6.6)	536 (6.3)	538 (6.3)	0.95 (0.84 to 1.07)	0.96 (0.85 to 1.08)
New diagnosis of diabetes*	366 (6.7)	399 (7.5)	323 (6.1)	1.12 (0.97 to 1.29)	0.91 (0.78 to 1.06)
Any heart failure	514 (6.0)	537 (6.3)	478 (5.6)	1.05 (0.93 to 1.19)	0.94 (0.83 to 1.07)
New atrial fibrillation†	570 (6.9)	550 (6.7)	537 (6.5)	0.97	0.96

				(0.86 to 1.09)	(0.85 to 1.07)
Renal impairment‡	871 (10.2)	906 (10.6)	1148 (13.5)	1.04 (0.96 to 1.14)	1.33§ (1.22 to 1.44)
Renal failure requiring dialysis	48 (0.6)	52 (0.6)	65 (0.8)	1.09 (0.74 to 1.61)	1.37 (0.94 to 1.98)

* Number of patients included in this analysis were 5427 in the ramipril arm, 5294 in the telmisartan arm, and 5280 in the combined therapy arm
† This category includes only patients who did not have atrial fibrillation at baseline: 8296 in the ramipril arm, 8259 in the telmisartan arm, and 8218 in the combination therapy arm
‡ No specific definitions were used. Renal impairment was determined based on a clinical investigator's report of an adverse event that led to the discontinuation of a study drug
§ p<0.001

When comparisons were made between the ramipril group and the telmisartan group, and between the combination therapy group and the ramipril group, very similar results were seen regarding the composite primary outcome. Telmisartan was not inferior to ramipril for both the prespecified composite primary outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure and for the primary outcome in the HOPE trial (death from cardiovascular causes, myocardial infarction, or stroke). When further analyses were adjusted for the patient's use of concomitant medications such as statins, antiplatelet agents, beta-blockers, diuretics, and calcium channel blockers, the results for both comparisons were consistent with these findings. Per protocol analyses showed a relative risk of 1.00 (95% CI, 0.92 to 1.09; p=0.006 for noninferiority) for the primary outcome with telmisartan compared to ramipril. Analyses of the combination therapy compared to ramipril showed results similar to the intent-to-treat analysis (relative risk, 0.98; 95% CI, 0.90 to 1.07).[3]

Safety:

Discontinuation of the study drug occurred in 2029 patients (23.7%) in the ramipril group and 1796 (21.0%) in the telmisartan group. Both drugs were discontinued in 1929 patients (22.7%) of the combination therapy group, and an additional 566 (6.7%) stopped taking one of the two drugs. More patients discontinued ramipril (either as monotherapy or with telmisartan) due to cough or angioedema as compared to telmisartan alone. The total number of discontinuations was significantly lower in the telmisartan group versus ramipril (p=0.02), but the absolute difference was considered modest because the active run-in phase selected patients for randomization only if they tolerated both medications. [3]

The number of patients who experienced a doubling of the creatinine level was similar in the three groups (159 in the ramipril group, 170 in the telmisartan group, and 180 in the combination therapy group). Also, an increase in the potassium level of more than 5.5 mmol per liter occurred similarly in the ramipril group (283 patients) and the telmisartan group (287 patients), but was significantly more frequent in the combination therapy group (480 patients, p<0.001 for the comparison between the combination therapy group and the ramipril group). [3]

The telmisartan group had lower rates of cough (1.1% vs. 4.2%, p<0.001) and angioedema (0.1% vs. 0.3%, p=0.01) when compared to the ramipril group, but a higher rate of hypotensive symptoms (2.6% vs. 1.7%, p<0.001); the rate of syncope was the same in the two groups (0.2%). Further, the ramipril group as compared to the combination-therapy group, showed a decreased risk of hypotensive symptoms (1.7% vs. 4.8%, p<0.001), syncope (0.2% vs. 0.3%, p=0.03), diarrhea (0.1% vs. 0.5%, p<0.001), and renal dysfunction (10.2% vs. 13.5%, p<0.001).[3]

Conclusion:

With respect to the primary outcome, telmisartan preserved about 95% of the benefits of ramipril over placebo and preserved about 105% of the benefits with respect to the primary outcome of death from cardiovascular causes, myocardial infarction, or stroke that were observed in the HOPE trial.[3]

The authors concluded that telmisartan was equivalent to ramipril in patients with vascular disease or high risk diabetes but do not have heart failure, and was associated with less cough and angioedema. The decision regarding which agent to use, telmisartan or ramipril, should depend on patient and physician preference and the patient's individual sensitivity to adverse events. The combination of the two drugs used in full doses in this patient population was associated with an increase in hypotensive symptoms, syncope, increased potassium level, and renal dysfunction, without an additional benefit.[3]

Further Subgroup Analyses:

There was also a comprehensive program of embedded substudies, in addition to the main ONTARGET endpoints, that evaluated the effect of the study medications on other aspects of cardiovascular disease. Ambulatory blood pressure monitoring was used to determine treatment effects of telmisartan and ramipril on cardiovascular morbidity and mortality after adjustment for 24-hour blood pressure. Furthermore, blood samples were obtained from the patients to examine new biochemical risk factors and genetic markers of cardiovascular disease.[2] In the future, analyses will be done to link genetic markers and risk factors to specific outcome findings. The biomarkers being evaluated in the sub-study include: cholesterol/lipid profile, glucose/HbA1c, C-reactive proteins, coagulation markers (fibrinogen, PAI, TPA), and genetic markers of CV disease presently unknown.[4] Magnetic resonance imaging was also employed to examine effects of treatment on cardiac structure and function during the study in relation to the emergence of left ventricular hypertrophy.[2] Also monitored were the effects of the treatments on the incidence and time course of erectile dysfunction.[2] Finally, health-economics data were gathered to determine resources used and direct medical costs associated with clinical events, and to evaluate the impact of treatment on patient preference (utility assessment) using the EuroQoL 5D questionnaire. The pharmacoeconomic study designs were cost-effectiveness and cost-utility analyses. The EuroQoL-5D was administered to the patients at baseline, at each 2-year follow-up visit, and at end of study.[2, 4] Results of the embedded substudies for ONTARGET will be compiled and available later in 2008.

References:

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Renoprotective Effects

Angiotensin receptor blockers (ARBs) are known to slow down the progression of diabetes related kidney disease, and in turn delay the time to onset of end-stage renal disease (ESRD). The ability of drugs to slow kidney disease progression can be monitored through rate of reduction in glomerular filtration rate (GFR), and the time it takes to arrive at ESRD. Level of proteinuria is an important surrogate endpoint often used in routine medical practice to monitor the severity of renal disease. ARBs and ACE inhibitors have shown beneficial effects on these markers. Several studies have been conducted to assess the effects of telmisartan at different stages of kidney disease in diabetic and non-diabetic patients. The results of these studies are presented below.

Bakris et al. (2007) conducted a prospective, randomized, double-blind, double-dummy, forced-titration, multicenter, parallel group, one-year treatment trial with an 8-week no-treatment follow-up period, comparing telmisartan and losartan in reducing proteinuria in hypertensive type 2 diabetic patients with overt nephropathy. Patients eligible for the study were required to have a SBP>130 mmHg, DBP>80 mmHg or be receiving antihypertensive medications, type 2 diabetes mellitus, morning spot urinary protein:creatinine [UPC] ≥700 mg/gCr, and serum creatinine ≤3.0 mg/dl in women and ≤3.2 mg/dl in men. For two weeks, patients were initiated on either telmisartan 40 mg or losartan 50 mg daily; then were forced titrated to telmisartan 80 mg and losartan 100 mg daily for an additional 50 weeks. Additional antihypertensive therapy (alpha or beta blocker, calcium channel blocker or diuretic) was also given to those patients whose blood pressure was not adequately controlled (>130 / >80 mmHg), to ensure that any treatment responses were not due to blood pressure differences. Vasodilators, other angiotensin receptor blockers, and ACE inhibitors were not permitted during the study. Eight hundred and sixty patients were randomized and 687 (80%) completed the study, which consisted of 124 centers in 10 countries. Baseline characteristics were similar for both groups; mean overall age was 60.3 years, and mean duration of diabetes was 14.3 years. The primary endpoint for this study was the change from baseline in morning spot UPC (mg/gCr) at one year. Telmisartan was superior to losartan on the primary endpoint (mean baseline): endpoint ratio 0.71 vs. 0.80 respectively, translating to the telmisartan group having a greater reduction from baseline protein/creatinine ratio (29%) versus the 20% reduction found in the losartan group. This difference is both statistically and clinically significant. Mean blood pressure reduction from baseline SBP/DBP was -4.8 / -3.2mmHg for telmisartan, and -2.7 / -2.9 mmHg for losartan. During the eight week no treatment follow-up period, UPC had risen to 80% of the baseline level. The increase in UPC from end of treatment to end of no treatment phases occurred mostly in the first 4 weeks, and than UPC stabilized on 80% of baseline. It is important to remember that a whole year had elapsed since baseline, in which a natural increase in UPC usually occurs. Adverse events, which were mainly mild to moderate in intensity, occurred in 84.0% patients receiving telmisartan, and 82.1% receiving losartan. These adverse events were consistent with the safety profiles of the two drugs, and with the expectations for patients suffering from hypertension, type 2 diabetes, and overt nephropathy.

Barnett et al. (2004) compared the renoprotective effects of telmisartan and enalapril in type 2 diabetics in a long term, randomized, double-blind, double-dummy, parallel-group trial. Patients included in the study had type 2 diabetes, SBP/DBP ≤180/95 mmHg, urinary albumin excretion rate >10 and <1000 µg/min at baseline, normal serum creatinine (≤1.6 mg/dl, normal glomerular filtration rate (GFR) (≥70 ml/min/1.73 m^2), and a normal renal ultrasound. Telmisartan (n=120) and enalapril (n=130) were initiated at 40 mg and 10 mg daily respectively for four weeks, and then increased to 80 mg and 20 mg daily. Optional dose reduction down to 40 mg daily and 10 mg daily at the investigator's discretion was allowed after 2 months, but no other dosing increases were made for the remainder of the study. The study primary endpoint was the change in GFR between baseline and the last available value during the five year study. GFR was assessed by measuring the plasma clearance of iohexol, considered a very accurate method. If no interventions were utilized, GFR in diabetic patients with proteinuria is known to decline at a rate of 10-12ml/min/1.73m^2 per year, resulting in a decline of 50-60ml/min/1.73m^2 over the five year study period. However, after 5 years, the change in the GFR was limited to -17.5 ml per minute/1.73 m^2 with telmisartan as compared with -15.0 ml per minute/1.73 m^2 with enalapril, demonstrating that telmisartan was not inferior to enalapril. Similarly, the results regarding the secondary endpoints for the study showed that the two agents were not considered significantly different. Also, none of the patients receiving either drug required dialysis or experienced

serum creatinine levels above 2.3mg/dl during the five year study. Discontinuation from the study due to adverse events occurred in 17% of patients receiving telmisartan and 23% receiving enalapril.

In another study, Galle et al. (2006) evaluated the effects on proteinuria of telmisartan 80 mg and valsartan 160 mg in hypertensive type 2 diabetic patients with overt nephropathy in a prospective, randomized, double-blind, double-dummy forced-titration, multicenter, parallel group, one-year treatment period. The 885 patients randomized were required to have type 2 diabetes mellitus, SBP>130 mmHg and/or DBP>80 mmHg, proteinuria ≥900 mg/24 hours, and serum creatinine of 1.1 - 3.0 mg/dL for females or 1.3 - 3.0 mg/dL for males. Patients were started on telmisartan 40 mg or valsartan 80 mg daily, and then forced titrated after 2 weeks to 80 mg of telmisartan and 160 mg of valsartan daily for an additional 50 weeks. Alpha or beta blockers, calcium channel blockers, and diuretics were allowed to provide blood pressure control (target <130/80 mmHg), in addition to the randomized study drug. The primary endpoint in the study was the change from baseline in 24-hour proteinuria after one year of treatment. The study results demonstrated non-inferiority of either drug, with a reduction in 24-hour proteinuria of 33% in both the telmisartan and valsartan groups. Composite endpoint rate (doubling of serum creatinine, end-stage renal disease or all cause mortality) study results were telmisartan 5.1% and valsartan 4.2%. Further analysis of the study data showed that in both treatment groups, greater efficacy was seen in patients with better blood pressure control, better diabetes control, and in patients who had not previously received an ARB or ACE inhibitor. A trend was also noted for superior efficacy in patients with greater proteinuria at baseline. 72.3% of patients receiving telmisartan, and 71.6% receiving valsartan experienced adverse events during the study, which tended to be mild. Incidences of discontinuations (mainly due to worsening of diabetic nephropathy, hypertension, or diabetes) were 3.2% for telmisartan, and 2.0% for valsartan.

Makino et al. (2007) evaluated whether telmisartan delays the progression of renal disease from incipient nephropathy to overt nephropathy in hypertensive or normotensive Japanese patients with type 2 diabetes mellitus. The study was a randomized, double-blind, placebo-controlled, multicenter, parallel group, one year treatment trial with an 8-week no-treatment follow-up period. Five hundred and twenty seven adult Japanese patients were randomized with diabetic nephropathy, presenting with microalbuminuria associated with type 2 diabetes mellitus, incipient nephropathy: urinary albumin-to-creatinine ratio (UACR) 100–300 mg/g, serum creatinine levels of <1.3 mg/dL (females) or <1.5 mg/dL (males), and were either normotensive or hypertensive. Sixty eight percent of patients were hypertensive at baseline, with a mean age of 61.7 years, and 73% were male. The telmisartan group was started on 20 mg daily for 2 weeks, and then forced titrated to 40 mg for an additional 2 weeks. Half of the telmisartan patients remained on 40 mg daily for another 48 weeks, and the other half were forced titrated to 80 mg daily for 48 weeks. Placebo was given daily for 52 weeks in the third group. The primary efficacy end point in the study was the transition rate from incipient to overt nephropathy [urinary albumin-to-creatinine ratio (UACR >300 mg/g)] and increase ≥30% from baseline at two consecutive visits. The resulting transition rates to overt nephropathy were found to be 16.7% for telmisartan 80 mg (n=168), 22.6% for telmisartan 40 mg (n=172), and 49.9% for placebo (n=174), (both telmisartan doses versus placebo, $p<0.0001$). Transition rates in normotensive patients were 11% for telmisartan 80 mg (n=51), 21% for telmisartan 40 mg (n=58), and 44.2% for placebo (n=54), (both telmisartan doses versus placebo, $p<0.01$). Telmisartan still showed a decreased in the transition rate to overt nephropathy, after adjustment for changes in systolic blood pressure. At final observation, telmisartan 80 mg and 40 mg reduced mean UACR by -58.8 and -37.9 mg/g, respectively, and placebo increased UACR by 40.9 mg/g (both telmisartan doses versus placebo, $p<0.0001$). For the secondary endpoint of patient normalization rates for microalbuminuria (urinary ACR <30mg/g creatinine), telmisartan 80 mg and 40 mg showed statistically significantly higher rates than the 0% rate for patients receiving placebo: 16.2% for telmisartan 80 mg and 7.5% for 40 mg. One or more adverse events was recorded in >90% of patients in each treatment group. Most of the adverse events were considered mild to moderate, and the frequency and severity of events was similar across treatment groups.

Sengul (2006) evaluated the long-term effects of dual blockade using lisinopril and telmisartan on blood pressure and albumin excretion rate (AER) in patients with type 2 diabetes. Eligible patients in the randomized, parallel-group, open-label, cross-over, prospective study were required to have type 2 diabetes, SBP ≥140 mmHg or DBP ≥90 mmHg, microalbuminuria (AER 30–300 mg/24 h), and be 40-65 years old with previously diagnosed hypertension despite ACE monotherapy for ≥6months. Telmisartan was initiated at 80 mg QD x 24 weeks, half the patients added lisinopril 20 mg for an additional 28 weeks. Lisinopril was initiated at 20 mg QD x 24 weeks, half the patients

added telmisartan 80 mg for an additional 28 weeks. The remaining patients continued with monotherapy for the additional 28 weeks. Hydrochlorothiazide (HCTZ) was added in both groups according to blood pressure throughout the study period (12.5 mg of HCTZ QD used by 19 telmisartan patients and 21 lisinopril patients). Significant ($p<0.001$) declines in SBP (-11.1 mmHg versus -10.0 mmHg), DBP (-5.6 mmHg versus -5.3 mmHg) and AER (98 mg/24 h versus 80 mg/24 h) were achieved with lisinopril (n = 95) or telmisartan (n = 97), respectively, after 24 weeks. Subsequent treatment with lisinopril plus telmisartan for 28 weeks resulted in further significant reductions ($p<0.001$) in SBP, DBP and AER compared with either monotherapy. Significant declines from baseline in AER were observed at 24 weeks, decreasing by 31.3% from a median of 256 mg/24 h (range 140–300 mg/24 h) to 176 mg/24 h (range 80–220 mg/24 h), ($p< 0.001$) with telmisartan, and by 37.1% from a median of 264 mg/24 h (range 150–300 mg/24 h) to 166 mg/24 h (range 90–220 mg/24 h) with lisinopril ($p< 0.001$). The difference between treatments was not significant ($p > 0.05$). From baseline to week 52, percentage reductions in AER with telmisartan, lisinopril, telmisartan plus lisinopril, and lisinopril plus telmisartan were 36.0, 40.5, 52.7 and 53.6%, respectively. AER was reduced to within the normal range (<30 mg/24 h) in eight patients in the lisinopril plus telmisartan group, and in seven patients in the telmisartan plus lisinopril group at 52 weeks. AER was not reduced within the normal range in either monotherapy group at 24 or 52 weeks. None of the patients receiving either monotherapy or combination therapy developed macroalbuminuria (AER >300 mg/24 h). All treatments were well tolerated. The most frequent adverse events were coughing, occurring exclusively in patients receiving lisinopril, and headache, which were experienced by less than 10% of the patients.

Aranda et al. (2005) studied the long term renoprotective effects of standard versus high dose telmisartan in hypertensive non-diabetic patients with biopsy-proven proteinuric nephropathies. Telmisartan 80 mg was administered once daily (standard) or twice daily (high) for two years. In the telmisartan standard dose group (n=40), serum creatinine increased from 1.6 to 2.7 mg/dl, and estimated creatinine clearance declined from 68 to 50ml/min. In the telmisartan 80 mg twice daily group (n=38), serum creatinine and estimated creatinine clearance did not change during the study. The decrease in proteinuria was more pronounced ($p<0.01$) in patients administered the high dose of telmisartan versus those patients administered the standard dose. Blood pressure control did not differ between the two groups during follow-up. Adverse event rates were similar between both groups, and no patients discontinued treatment due to adverse events.

Vogt et al. (2005) examined the effect of telmisartan or hydrochlorothiazide on the control of urinary albumin excretion (UAE) in patients with isolated systolic hypertension. Eligible patients for the double-blind, placebo-controlled, parallel-group study, with a seated SBP/DBP 150–179/<90 mmHg were randomized to one of five treatment regimens: telmisartan 20 mg, 40 mg, or 80 mg daily, HCTZ 12.5 daily, or placebo daily. After 6 weeks of telmisartan treatment, the median (95% CI) reductions in UAE with telmisartan 20, 40 and 80 mg were 0.8 mg/l (95% CI 0.5, 1.8), 1.2 mg/l (95% CI 0.6, 2.1) and 0.3 mg/l (95% CI 0.0, 1.0), respectively. A dose response was not observed for either UAE or SBP, so the values of the three telmisartan groups were combined for comparison with hydrochlorothiazide and placebo. In the telmisartan group (all doses combined, n=354)), a median reduction in UAE from a baseline of -14.1% was observed versus -1.1% and -2.7% in the hydrochlorothiazide (n=140) and placebo (n=120) groups, respectively. The difference between telmisartan and hydrochlorothiazide was significant ($p = 0.017$). Reductions in UAE with telmisartan were observed in patients with baseline normoalbuminuria, microalbuminuria or macroalbuminuria. Telmisartan and hydrochlorothiazide produced comparable reductions in systolic blood pressure in these patients. The larger effect of telmisartan was independent of blood pressure differences between telmisartan and hydrochlorothiazide. The rates of the five most common adverse events were comparable among the three treatment groups (headache, bronchitis, upper respiratory tract infection, back pain, and Influenza-like symptoms.

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TRENDY Trial

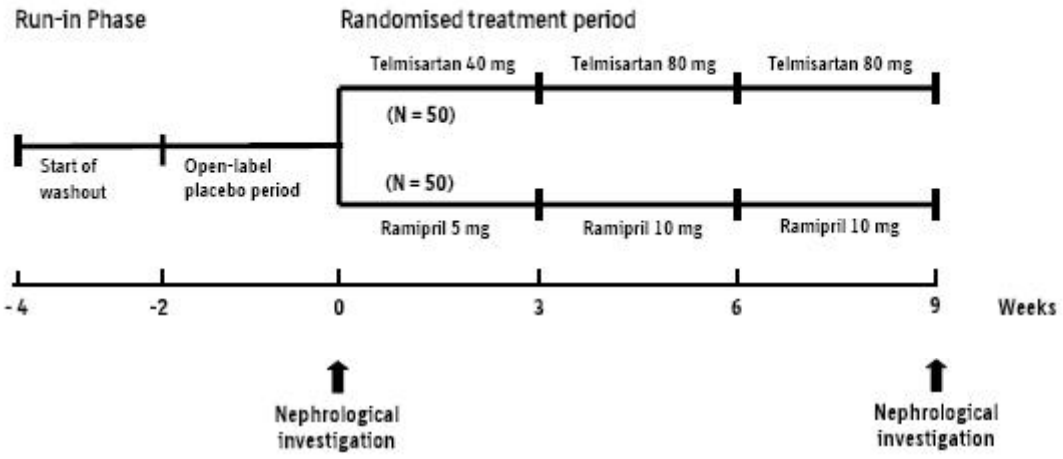
TRENDY (Telmisartan versus Ramipril in renal ENdothelial Dysfunction) was a prospective, randomized, double-blind, double-dummy, forced titration, parallel group, multicenter trial to compare the effects of either telmisartan (40-80 mg p.o. once daily) or ramipril (5-10 mg p.o. once daily) on renal endothelial dysfunction in hypertensive patients with type 2 diabetes and normoalbuminuria or microalbuminuria over a treatment period of 9 weeks.[1-3]

Functional integrity of the endothelium is crucial for the maintenance of blood flow and antithrombotic capacity.[1-3] It is now clear that impaired endothelial function contributes substantially to cardiovascular disorders and emerging evidence indicates that locally generated vasoactive substances such as nitric oxide (NO) and angiotensin II are important determinants of the natural history of vascular disease. The endothelium releases humoral factors that control relaxation and contraction, thrombogenesis and fibrinolysis, as well as platelet activation and inhibition.[4-8] One important factor released by the endothelium is nitric oxide (NO), which is formed from L-arginine by action of NO synthase. NO is a potent vasodilator and inhibitor of platelet aggregation; it also exhibits antifibrotic activity.[2,8] Treatment with ACE inhibitors increases the levels of bradykinin, which exerts vasodilatory effects by stimulating NO and cyclic guanosine monophosphate (cGMP) production, as well as release of prostaglandin E_2 and prostacyclin.[9] ACE inhibitors have been found to increase NO production in the coronary vasculature.[9,10] Angiotensin II, produced by actions of renin and angiotensin-converting enzyme (ACE), contributes to the development of atherosclerosis and promotes cardiovascular remodeling and fibrosis.[1] Activation of the AT_1 receptor by angiotensin II, in addition to vasoconstriction and increased blood pressure, has been shown to cause superoxide radical release, which causes increased oxidative stress leading to NO breakdown and endothelial dysfunction.[1-3] On the other hand, stimulation of the AT_2 receptor has been reported to counteract many actions of the AT_1 receptor leading to vasodilation by stimulating production of bradykinin and NO.[2,9] In addition, blockade of the AT_1 receptor with an ARB causes increased stimulation of the AT_2-receptor leading to effects such as vasodilation and tissue regeneration.[11]

The primary efficacy endpoint of the TRENDY trial was the change from baseline of renal plasma flow (RPF) in response to N-monomethyl-L-arginine (L-NMMA) infusion at the end of treatment.[1-3] L-NMMA is a bioactive compound that inhibits the synthesis of NO in a dose-dependent fashion. Intra-venous or intra-arterial injections of L-NMMA produce a powerful and prolonged vasoconstrictor effect, which can be reversed by L-arginine in a dose-dependent manner. By infusion of L-NMMA, the synthesis of NO in the systemic and renal vasculature was inhibited and thus the contribution of NO to RPF could be analyzed. RPF was measured by determining the renal clearance of para-aminohippuric (PAH), a substance that is completely removed from the blood in a single pass through the kidney.[3]

Ninety six patients (47 in the telmisartan and 49 in the ramipril group) were randomized into the trial. Primary inclusion criteria were: hypertension (seated SBP/DBP 140-180/90-110 mmHg), age 30-80 years-old, type 2 diabetes, normo- or microalbuminuria, and glomerular filtration rate (GFR) > 80 mL/min. The exclusion criteria included patients with type 1 diabetes, type 2 diabetes requiring the administration of insulin and/or glitazones, hyperlipidemia necessitating statin therapy, overt proteinuria, proliferative retinopathy, active coronary artery disease, congestive heart failure NYHA III or IV, and hepatic dysfunction.[1-3] As depicted in Figure 1, prior to randomization, patients were washed out of any ACE inhibitor or ARB medication for at least 4 weeks. Following the washout period, patients received open-label placebo for 2 weeks. Patients then were randomized to receive either 40 mg telmisartan or 5 mg ramipril once daily for 3 weeks. At 3 weeks, patients were uptitrated to 80 mg telmisartan or 10 mg ramipril for another 6 weeks.[3]

Figure 1.



At baseline, RPF was comparable between the treatment groups. RPF was reduced by infusion with L-NMMA both at baseline and at Week 9, with a larger reduction at Week 9. The mean change from baseline was -43.2 mL/min in the telmisartan group, and -26.1 mL/min in the ramipril group (adjusted means). Changes from baseline to Week 9 were significant for both treatment groups (telmisartan: $p<0.001$, ramipril: $p=0.018$). This result shows that 9 weeks of treatment with either telmisartan or ramipril improved the basal activity of NO in the renal vasculature. Comparison of the 2 treatment groups yielded a difference of -17.1 mL/min for the adjusted mean. Although telmisartan had a slightly larger effect than ramipril, this difference was not statistically significant ($p=0.214$). Thus, telmisartan and ramipril did not differ in their effect on the basal NO release in the renal vasculature after a 9-week treatment.[1-3, 12]

In addition, after 9 weeks of treatment, both telmisartan and ramipril produced an increase in RPF. This change was statistically significant for telmisartan ($p<0.05$) but not for ramipril ($p=0.221$). Also, both treatments produced a decrease in renal vascular resistance, which was statistically significant for telmisartan ($p=0.010$) but not for ramipril ($p=0.119$).[1-3, 12]

Adverse events were reported by 25.5% of patients in the telmisartan group and by 24.5% in the ramipril group. Drug-related adverse events were reported by 4 patients (8.2%) receiving ramipril (dizziness in 2 patients, headache, and cough) and by no patient receiving telmisartan. Serious adverse events occurred in 3 patients (3.1%): 1 in the telmisartan group, 1 in the ramipril group, and 1 patient during the placebo run-in phase. None of these were considered to be drug-related. With respect to blood chemistry and hematology parameters, no safety concerns were identified.[12]

Overall, the TRENDY trial confirmed the positive effect of both telmisartan and ramipril on renal endothelial function, demonstrated by increased NO production and release. No deleterious effects on kidney function were observed during the 9-week treatment phase, and the favorable safety profile of telmisartan and ramipril was confirmed in this study.

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